REMARKS

Claims 19-22, 24, 30-31, and 49-54 are currently pending in this application. Claims 19, 30, and 31 have been amended. The amendments to claims 19, 30, and 31 do not constitute new matter.

Rejection of Claims 19-22, 30-31, and 49-54 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 19-22, 30-31, and 49-54 under 35 U.S.C. § 103(a) as obvious over Waldrep *et al.* (U.S. Patent No. 5,958,378) ("Waldrep") and Fujii *et al.* (U.S. Patent No. 6,197,829) ("Fujii"), in view of Adjei *et al.* (U.S. Patent No. 5,635,161) ("Adjei"), Knight *et al.* (U.S. Patent No. 5,049,388) ("Knight"), Gordon *et al.* (U.S. Patent No. 6,672,893) ("Gordon"), Iacono *et al.* (*Am. J. Respir. Care Med.*, 1997, 155:1690-1698) ("Iacono 1997"), and further in view of Stanford et al. (EP 0372 541) ("Stanford").

The Examiner contends that Waldrep and Fujii teach "that cyclosporine is old and well known in combination with various pharmaceutical carriers... particularly, aerosol dosage form." The Examiner also contends that "[t]hese medicaments are taught as useful as immunosuppressant [*sic*] for treating or preventing graft rejections, inflammation and other immunological [*sic*] mediated conditions. . .". The Examiner argues that Adjei teaches that pulmonary delivery of peptide and protein biotherapeutics, such as cyclosporin, by aerosol is well known in the art, that Knight teaches that cyclosporine aerosol dosage may be in powder form, and that Gordon discloses that dry powder is a well known form for pulmonary delivery. The Examiner states that Iacono 1997 teaches a cyclosporine composition for the treatment of graft rejection. Lastly, the Examiner states that Stanford teaches that immunosuppressive agents are "known to be useful for reducing the frequency of acute transplant rejections."

The Examiner has further rejected claim 24 under 35 U.S.C. § 103(a) as obvious over Waldrep and Fuji, in view of Adjei, Knight, Gordon, and Iacono 1997, and further in view of Armistead *et al.* (U.S. Patent No. 5,665,774) ("Armistead"). The Examiner relies upon the reasoning set forth above, and relies on Armistead as teaching that "steroid is useful in treating or preventing graft rejection."

The Examiner asserts that it would have been *prima facie* obvious to a person of ordinary skill in the art to combine the cited references to reach the present invention. The Examiner states that a person of ordinary skill in the art would be motivated to treat patients prior to the development of symptoms associated with transplant rejection with an aerosol dosage form of cyclosporin "because cyclosporin are [*sic*] known to be useful for organ transplantation patients. . .".

Applicant respectfully traverses the foregoing rejection. Applicant respectfully submits that the cited references, alone or in combination, simply do not teach or suggest each of the elements of the claimed invention. The cited references fail to teach or suggest *prevention* of *chronic refractory graft rejection* by administering aerosolized cyclosporine to a patient *prior to the development of symptoms*, but rather teach the treatment of *acute graft rejection after symptoms of persistent acute rejection are evident*.

The Examiner asserts that the particular timing of administration of a therapeutic agent "would have been in the purview of one of ordinary skill in the art." Therefore, the Examiner seems to conclude that administering inhaled cycolsporine as a prophylactic prior to development of symptoms would have been obvious, even though there is *no teaching or suggestion* in any of the cited references to use cyclosporine prior to the development of symptoms.

Applicant respectfully submits that prophylactic treatment of transplantation patients with cyclosporine would not have been obvious to one of ordinary skill in the art at the time the invention was made. In particular, when human lung transplant recipients receive standard immunosuppressive therapy consisting of one or more of oral cyclosporine, tacrolimus, and prednisone, the suggestion that they also be treated with an aerosolized composition comprising a therapeutic dose of cyclosporine *before any symptoms are evident* is not obvious, nor would it have be predicted to provide additional benefit prior to the instant invention. Aerosolized cyclosporine is potent, fairly toxic, and an acute irritant in conjunction with the vehicle employed to deliver the drug is not well tolerated by patients. As described in Gilbert *et al.* (*Am. J. Respir. Crit. Care Med.*, 1997, vol. 156:1789) ("Gilbert"; Exhibit B), inhalation of cyclosporine liposome aerosols resulted in coughing and tracheal irritation in the majority (8 of 10)

volunteers. (See the Abstract and page 1792). In Gilbert, liposomal cyclosporine was investigated as a treatment for moderately severe asthma. Furthermore, Stanford specifically states that "use of cyclosporine can cause significant kidney damage for patients receiving organ transplants" when administered systemically and only teaches the use of cyclosporine in combination with another agent for the treatment of acute rejection in order to mitigate the toxicity of cyclosporine alone (see page 2 of Stanford). This statement teaches away from the use of cyclosporine alone, especially prior to development of any symptoms. In addition, administration of cyclosporine as an aerosol is a cumbersome delivery system that is inconvenient to patients and hospital staff alike. The Examiner has not provided evidence to support the *pre-symptom intervention* with a non-standard form of cyclosporine treatment to treat chronic refractory lung transplant rejection, as presently claimed. Timing of drug administration is not a trivial matter, and is often the subject matter of long and costly clinical trials even when treating symptomatic disease. The current claims are directed to prophylactic treatment of a chronic condition.

With respect to the recitation of "preventing chronic refractory graft rejection" in the claims, the Examiner states that "it is noted that a method known for preventing transplantation rejections would reasonably [*sic*] expected to prevent the development of rejections, either chronic or acute." This statement is simply not true and the Examiner provides no evidence to the contrary.

The Examiner has stated that the phrase "preventing chronic refractory graft rejection" appears in the preamble and therefore is not accorded patentable weight. While Applicant respectfully disagrees with the Examiner's statement, Applicant notes that claims 19, 30, and 31 have been amended herein such that the phrase "preventing chronic refractory graft rejection" is recited in the body of the claims. Therefore, the phrase must be accorded patentable weight.

The disclosure that aerosolized cyclosporine may be used as a treatment for acute rejection does not lead to a reasonable expectation that aerosolized cyclosporine will be successful in preventing chronic refractory rejection. As set forth in the previous Amendment and Response dated June 5, 2007, the mechanism underlying chronic rejection, as opposed to

acute rejection, is not known. For example, DeCamp, Jr., *N. Engl. J. Med.*, 2006, 354:191-193 ("DeCamp") states:

> Whereas the mechanism of acute rejection in solid-organ transplantation is well understood as an inflammatory response to allo-antigen stimulation mediated by T lymphocytes, neither the triggers nor the mechanisms of chronic rejection are known.

DeCamp at page 192, left column (emphasis added). Thus, DeCamp demonstrates that in 2006, and therefore at the time of filing of the present application, the mechanisms underlying chronic rejection were unknown. Due to the lack of knowledge regarding the mechanisms behind chronic rejection, a person of ordinary skill in the art could not reasonably conclude that modifying the timing of the administration, based upon data regarding treatment of persistent acute graft rejection after it becomes evident, would suggest that pre-symptomatic treatment would be effective in the prevention of chronic refractory graft rejection. Indeed, Iacono 1997 is directed to the treatment of patients who are already experiencing symptoms of "persistent acute" rejection, and therefore teaches away from both administration prior to the development of symptoms associated with acute transplant rejection and administration to prevent chronic refractory graft rejection.

Furthermore, subsequent studies carried out after the filing of the present invention have shown that aerosolized cyclosporine is not equally effective in the treatment of acute graft rejection and chronic refractory graft rejection. In particular, Iacono et al., 2006, "A Randomized Trial of Inhaled Cyclosporine in Lung-Transplant Recipients," *N. Engl. J. Med.* 354:141-150 (Iacono 2006), as provided to the Examiner with Applicant's Amendment and Response dated August 26, 2006, describes a clinical trial involving inhaled cyclosporine, and states that "[i]nhaled cyclosporins did not improve the rate of acute rejection, but it did improve survival and extend periods of chronic rejection-free survival." (see page 141, last para.). Furthermore, in discussing these results, Iacono 2006 states, in the paragraph bridging pages 148 and 149:

> Chronic rejection remains the leading cause of death after lung transplantation despite the use of systemic calcineurin inhibitors [citations]. The immunosuppressive effects of cyclosporine have been shown to be dose-dependent. However, high systemic levels of the drug cannot be achieved without significant toxicity, especially to the kidneys. We hypothesized that the

> inhalation of an aerosol cyclocporine would provide high pulmonary concentrations of the drug with minimal systemic toxicity, resulting in less acute and chronic rejection. *This double-blind, placebo-controlled trial of inhaled cyclosporine given in addition to conventional immunosuppression after lung transplantation was negative with respect to its primary end point, since rates of acute rejection were similar in the group receiving cyclosporine and that receiving placebo. However, survival improved significantly with aerosol cyclosporine, as did the rate of chronic rejection-free survival (on the basis of both histologic and spirometric analysis).* (Emphasis added)

Furthermore, in a review of Iacono 2006 (Merriman, J. "Inhaled Cyclosporine Preserves Posttransplant Lung Function," *PulmonaryReviews.com*, 2006, Vol. 11, No. 7) ("Merriman;" Exhibit A), describes a presentation by Dr. Iacono at the annual meeting of the American Thoracic Society on May 23, 2006, and states that "Iacono and colleagues had previously reported that while inhaled cyclosporine did not improve the rate of acute rejection, it did improve survival and extend periods of chronic rejection-free survival on the basis of both histologic and spirometric analysis." (see page 2). Furthermore, also at page 2 of the article, Dr. Iacono is quoted as stating:

> In the absence of notable differences in rates of acute rejection, a positive result in terms of chronic rejection was unexpected, since previous studies have linked repeated acute rejection events with chronic rejection. . . Histologically, chronic rejection presents in the airways as bronchiolitis obliterans, whereas acute rejection presents as vasculitis. Bronchioles would have higher local concentrations of a drug as a result of direct aerosol delivery, whereas pharmacokinetic studies suggest a much less substantial vascular concentration of the drug. Therefore, it is possible that aerosol cyclosporine has a local airway anti-inflammatory effect that decreases the likelihood of chronic rejection while having a lesser effect on vascular acute rejection.

Therefore, based on all of the above evidence, it is clear that the disclosure that aerosolized cyclosporine may be used as a treatment for acute rejection does not lead to a reasonable expectation that aerosolized cyclosporine will successfully prevent chronic refractory rejection.

Applicant reiterates the arguments set forth in the Amendment and Response of August 26, 2006 relating to the fact that the clinical benefits of prophylactic aerosolized cyclosporine were received with enthusiasm by the scientific community and were *not* regarded as obvious old

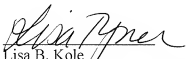
news, and respectfully requests that the Examiner consider these arguments and the evidence provided therewith. Applicant reminds the Examiner that that the evidence of non-obviousness presented here and in the previous Responses must be considered in evaluating the patentability of the presently claimed invention.

Based on the foregoing, Applicant respectfully submits that the presently claimed invention is not obvious in view of the cited art. Reconsideration and withdrawal of the instant rejection is respectfully requested.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. The Applicant believes that the invention described and defined by claims 19-22, 24, 30-31, and 49-54 are patentable over the rejections of the Examiner. Withdrawal of all rejections and reconsideration of the amended claims is requested.

Respectfully submitted,



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